UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,011	06/20/2003	Ciaran N. Cronin	SYR-AIK-5001-C1	5098

32793 7590 12/19/2007

TAKEDA SAN DIEGO, INC.
10410 SCIENCE CENTER DRIVE
SAN DIEGO, CA 92121

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
12/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,011	CRONIN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,9,12,15,17,18,22-25 and 27-36* is/are pending in the application.

4a) Of the above claim(s) *18 and 22-25* is/are withdrawn from consideration.

5)☒ Claim(s) *17,30,31 and 34-36* is/are allowed.

6)☒ Claim(s) *1,4,9,12,15,27-29,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/15/07 has been entered.

[2] Claims 1, 4, 9, 12, 15, 17-18, 22-25, and 27-36 are pending in the application.

[3] Applicant's amendment to the claims, filed on 10/15/07, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's amendment to the specification, filed on 10/15/07, is acknowledged.

[5] Receipt of a Statement of Substance of Interview, filed on 11/15/07, is acknowledged.

[6] Applicant's arguments filed on 10/15/07, in response to the Office actions mailed on 6/12/07 and 9/14/07 have been fully considered and are deemed to be persuasive to overcome the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[7] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Election/Restriction

[8] Claims 18 and 22-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/31/06.

Specification/Informalities

[9] The objection to the specification as being inconsistent in identifying the amino acid sequence of the atomic coordinate listing of Figure 3 as SEQ ID NO:1 is maintained for the reasons set forth below.

RESPONSE TO ARGUMENT: Applicant argues that in view of the specification's disclosure at paragraph 108 (as amended in the instant specification amendment), "FIG. 3 accurately represents the atomic coordinate listing of the amino acid sequence set forth in SEQ ID NO: 1".

Applicant's argument is not found persuasive. Initially, it is noted that although not expressly stated in the specification, it appears the protein used in the crystallization is a protein consisting of amino acids 24-295 of SEQ ID NO:3, since that protein was prepared and concentrated as disclosed at p. 47 paragraphs 195-196 of the specification. If a protein other than a protein consisting of amino acids 24-295 of SEQ ID NO:3 was used in the crystallization, applicant is requested to so state and clarify the record. Since a protein consisting of amino acids 24-295 of SEQ ID NO:3 appears to have been used in the crystallization and amino acids 24-295 of SEQ ID NO:3 are distinct in sequence from SEQ ID NO:1, it would appear that the sequence of amino

acids as set forth in the atomic coordinates of Figure 3 is not SEQ ID NO:1. Furthermore, the sequence of amino acids as set forth in the atomic coordinates of Figure 3 appears to be a subsequence of SEQ ID NO:1, not SEQ ID NO:1 itself as suggested by labeling the sequence of amino acids as set forth in the atomic coordinates of Figure 3 as being SEQ ID NO:1. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

[10] Claims 9, 12, 15, 27-29, and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 9 (claims 12, 15, and 27-29 dependent therefrom) and 33 are confusing in the recitation of "wherein the protein crystal has a crystal lattice..." prior to the step of "storing the crystallization volume..." In view of this recitation, it appears the protein-ligand crystal is already present in the crystallization volume prior to the "storing the crystallization volume..." crystallization step. It is suggested that applicant clarify the meaning of the claims.

[b] Claim 12 (claims dependent therefrom) is confusing in the recitation of "the protein diffracts X-rays..for a determination of structure coordinates" as it is known in the art that it is the protein crystal – not the protein itself – that diffracts X-rays for structure determination. It is suggested the applicant clarify the meaning of the claim.

[c] Claim 29 recites the limitation "the one or more entities". There is insufficient antecedent basis for this limitation in the claim. It is suggested that claim 29 be amended to depend from claim 28.

Claim Rejections - 35 USC § 112, First Paragraph

[11] The new matter rejection of claims 31-33 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's submission filed on 9/4/07, which includes the reference of Polayes et al. (Life Technology Focus 18:2-5), describing the recognition site of TEV protease as Glu-Asn-Leu-Tyr-Phe-Gln*Gly (p. 2 column 1). As SEQ ID NO:3 has such a recognition site at amino acids 18-24, a skilled artisan would recognize that cleavage of SEQ ID NO:3 by rTEV protease as disclosed in the specification at p. 47, paragraph 196 would remove the first 23 amino acids of SEQ ID NO:3, resulting in a polypeptide with an N-terminal deletion of the first 23 amino acids of SEQ ID NO:3. Since SEQ ID NO:3 is a 295 amino acid polypeptide, the resulting polypeptide would be amino acids 24-295 of SEQ ID NO:3.

[12] The written description rejection of claim(s) 17 and 30-31 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment to the claims, limiting the recited polypeptide to being "non-crystalline".

[13] The written description rejection of claim(s) 1, 4, 9, 12, 15, 27-29, and 32-33 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the

reasons stated below. The rejection was fully explained in the prior Office action. See paragraph 10 beginning at p. 4, bottom of the Office action mailed on 6/12/07.

RESPONSE TO ARGUMENT: Regarding claims 1 and 9, applicant argues (beginning at the top of p. 9 of the instant remarks) the rejection is obviated by claim amendment, apparently to recite "wherein said protein is in complex with an ATP-binding site ligand."

Applicant's argument is not found persuasive. The examiner acknowledges the amendment to claims 1, 9, 32, and 33 to limit the protein of the crystalline form to being in complex with a genus of "ATP-binding site ligand[s]". It is noted that even though the ligand is defined in the claim as an "ATP-binding site ligand", the claim does not require that the "ligand" be bound to the ATP-binding site of the recited protein and the structures of the "ATP-binding site ligand[s]" as encompassed by the genus are undefined and unlimited. Consequently, the genus of crystals is seen as encompassing widely variant species, encompassing a crystal of a protein as encompassed by the claims in complex with any "ATP-binding site ligand" having any structure. In this case, the specification discloses only a single disclosed species of crystals, *i.e.,* a crystal of residues 24-295 of SEQ ID NO:3 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6) and method for its crystallization, *i.e.,* the method disclosed at p. 48, ¶¶ [00198] and [0199] of the specification. While applicant may argue that a skilled artisan would expect that co-crystallizing the recited protein in complex with any other "ATP-binding site ligand" under the disclosed conditions would result in a crystal as encompassed by the

claims, there is no evidence of record to support this position and the state of the art at the time of the invention would suggest otherwise. For example, a common method of obtaining a crystal with a ligand other than that of an initial crystal is to soak a crystal of a liganded protein with a different ligand. However, without analysis of the resulting crystal, there is no way to predict *a priori* whether the resulting crystal will maintain the space group and unit cell dimensions of the parent crystal prior to ligand soaking. See, *e.g.,* Skarzynski et al. (*Acta Crystallogr D Biol Crystallogr* D62:102-107), which discloses, "crystals of complexes obtained by compound soaking may become damaged, change their diffraction properties or even change the space group during the soaking experiment" (p. 103, column 2, middle).

Regarding claims 32-33, applicant argues (beginning at the middle of p. 9 of the instant remarks) the specification discloses the representative species of a crystal of SEQ ID NO:3 and its method of crystallization and based on the level of knowledge at the time of the invention, a skilled artisan would be able to "make the necessary adjustments to the experimental conditions to arrive at the appropriate crystallization conditions for a protein of residues 24-295 of SEQ ID NO:3. Applicant argues a Google search yields a large number of hits for protein crystallization methods and thus it is "quite clear that the level of skill in the art was high" in the art of protein crystallography.

Applicant's argument is not found persuasive. Although not expressly stated in the specification, it appears that the protein used in the crystallization is amino acids 24-295 of SEQ ID NO:3, since that protein was prepared and concentrated as disclosed at p. 47 paragraphs 195-196 of the specification. If a protein other than a protein

consisting of amino acids 24-295 of SEQ ID NO:3 was used in the crystallization, applicant is requested to so state and clarify the record. In prior Office actions, the examiner stated that the specification disclosed the representative species of a crystal of a protein consisting of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6). However, upon further consideration and in view of the specification's disclosure, it is the examiner's position that the specification does not disclose the representative species of a crystal of a protein consisting of residues 125-391 of SEQ ID NO:1. Instead, the specification discloses the representative species of a crystal of residues 24-295 of SEQ ID NO:3 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6). As such, the reasoning previously applied to claims 32-33 for lack of adequate written description will now be applied to claims 1 (claim 4 dependent therefrom) and 9 (claims 12, 15, and 27-29 dependent therefrom) as set forth below.

The specification fails to disclose even a single representative species of crystals and methods as encompassed by claims 1 (claim 4 dependent therefrom) and 9 (claims 12, 15, and 27-29 dependent therefrom). As evidenced by the amino acid sequence alignment of Appendix A of the Office action mailed on 6/12/07, residues 24-295 of SEQ ID NO:3 have an N-terminal extension relative to residues 125-391 of SEQ ID NO:1, thus, the proteins are distinct in their respective amino acid sequences. While applicant asserts that because methods of protein crystallization were known in the art, a skilled artisan would be able to "make the necessary adjustments to the experimental

conditions to arrive at the appropriate crystallization conditions" for a structurally related protein. While there is no dispute that methods for protein crystallization were known, the state of the art at the time of the invention indicates that protein crystallization was highly unpredictable. For example, a reference cited by applicant in support of their position, Drenth ("Principles of X-Ray Crystallography", Second Edition, Springer, New York, NY, 1999) teaches "Obtaining suitable single crystals is the least understood step in X-ray structural analysis of a protein. The science of protein crystallization is an underdeveloped area...Protein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20; cited in the Office action mailed on 4/4/06), which teaches that "each protein crystallizes under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). See also the teachings of McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990), which states (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. *Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids*" (emphasis added). Table 2 is a list of 25

different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual." Thus, in view of these teachings, a skilled artisan would recognize there is a *high* level of unpredictability in making a protein crystal.

As such, even though the disclosed crystal is of a polypeptide that shares a substantial structural feature with the polypeptide of residues 125-391 of SEQ ID NO:1, there is no way to predict whether such a crystal of residues 125-391 of SEQ ID NO:1 would crystallize under the same conditions to achieve a crystal having the identical space group and unit cell dimensions.

Other than the single species as noted above, the specification fails to describe any other compositions or crystals or methods for crystallization thereof as encompassed by the claims. MPEP § 2163 states "[f]or inventions in an unpredictable

art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." As such, the single disclosed species of compositions and crystals and methods for making said crystal as noted above fail to adequately describe all compositions, crystals, and methods as encompassed by the claims. Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

At least for the reasons of record and reasons stated herein, the specification fails to adequately describe the claimed invention.

[14] The scope of enablement rejection of claim(s) 17 and 30-31 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendment to the claims, limiting the recited polypeptide to being "non-crystalline".

[15] The scope of enablement rejection of claim(s) 1, 4, 9, 12, 15, and 27-29 under 35 U.S.C. 112, first paragraph, is withdrawn in favor of the enablement rejection as set forth below.

[16] Claims 1, 4, 9, 12, 15, and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Although not expressly stated in the specification, it appears that the protein used in the disclosed crystallization method at p. 48 of the specification is a protein consisting of amino acids 24-295 of SEQ ID NO:3, since that protein was prepared and concentrated as disclosed at p. 47 paragraphs 195-196 of the specification. In prior Office actions, the examiner stated that the specification disclosed the working example of a crystal of a protein consisting of residues 125-391 of SEQ ID NO:1 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6). However, upon further consideration and in view of the specification's disclosure, it is the examiner's position that the specification does not disclose the working example of a crystal of a protein consisting of residues 125-391 of SEQ ID NO:1. Instead, in view of the specification's disclosure as noted above, the specification discloses the working example of a crystal of a protein consisting of residues 24-295 of SEQ ID NO:3 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6). As such, the reasoning previously applied to claims 32-33 for lack of an enabling disclosure for the full scope of the claims will now be applied to claims 1 (claim 4 dependent therefrom) and 9 (claims 12, 15, and 27-29 dependent therefrom) as set forth below.

As noted above, the specification discloses only a single working example of a crystal, *i.e.,* a crystal of a protein consisting of residues 24-295 of SEQ ID NO:3 in

complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6). Other than this single working example, the specification fails to provide any specific guidance for crystallizing a polypeptide consisting of amino acids 125-391 of SEQ ID NO:1 with an expectation of achieving a diffraction-quality crystal that maintains the recited space group and unit cell dimensions. Put another way, the specification fails to disclose even a single working example of a crystal and method as encompassed by claims 1 (claim 4 dependent therefrom) and 9 (claims 12, 15, and 27-29 dependent therefrom). As evidenced by the amino acid sequence alignment of Appendix A of the Office action mailed on 6/12/07, residues 24-295 of SEQ ID NO:3 have an N-terminal extension relative to residues 125-391 of SEQ ID NO:1, thus, the proteins are distinct in their respective amino acid sequences. While the examiner acknowledges that "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed" (MPEP 2164.02), it is noted that "Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art". While methods for protein crystallization were known, the state of the art at the time of the invention indicates that protein crystallization was highly unpredictable. See the noted teachings of Drenth, Kierzek et al., and McPherson set forth above. See also the noted teachings of Branden (cited in the 4/4/06 Office action at pp. 9-10) and Buts et al. (cited in the 9/22/06 Office action at p. 11). Thus, in view of these teachings, a skilled artisan would recognize there is a *high* level of unpredictability that conditions that are successful in crystallizing a first protein will achieve

crystallization of a second protein, even a second protein that is structurally related to the fist protein.

As such, even though the disclosed crystal is of a polypeptide that shares a substantial structural feature with the polypeptide of residues 125-391 of SEQ ID NO:1, there is no way to predict whether such a crystal of residues 125-391 of SEQ ID NO:1 would crystallize under the same conditions to achieve a crystal having the identical space group and unit cell dimensions.

In view of the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

RESPONSE TO ARGUMENT: To the extent applicant's argument applies to the instant rejection, the argument is addressed below. Applicant argues (beginning at the

middle of p. 9 of the instant remarks) the specification discloses the representative species of a crystal of SEQ ID NO:3 and its method of crystallization and based on the level of knowledge at the time of the invention, a skilled artisan would be able to "make the necessary adjustments to the experimental conditions to arrive at the appropriate crystallization conditions for a protein of residues 24-295 of SEQ ID NO:3. Applicant argues a Google search yields a large number of hits for protein crystallization methods and thus it is "quite clear that the level of skill in the art was high" in the art of protein crystallography.

Applicant's argument is not found persuasive. While applicant asserts that because methods of protein crystallization were known in the art, the level of skill in the art is high and a skilled artisan would be able to "make the necessary adjustments to the experimental conditions [of the disclosed working example] to arrive at the appropriate crystallization conditions" for a structurally related protein. While there is no dispute that methods for protein crystallization were known, the state of the art at the time of the invention indicates that protein crystallization was highly unpredictable. See the noted teachings of Drenth, Kierzek et al., and McPherson set forth above and the noted teachings of Branden (cited in the 4/4/06 Office action at pp. 9-10) and Buts et al. (cited in the 9/22/06 Office action at p. 11). In view of the detailed analysis of the Factors of *In re Wands* as set forth above, it is the examiner's position that the specification fails to enable the crystal and methods as set forth in the claims.

[17] The scope of enablement rejection of claim(s) 32-33 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in the prior Office action. See paragraph 11 beginning at p. 8 of the Office action mailed on 6/12/07.

RESPONSE TO ARGUMENT: Applicant argues (beginning at the top of p. 9 of the instant remarks) the rejection is obviated by claim amendment, apparently to recite "wherein said protein is in complex with an ATP-binding site ligand."

Applicant's argument is not found persuasive. The examiner acknowledges the amendment to claims 32 and 33 to limit the protein of the crystalline form to being in complex with a genus of "ATP-binding site ligand[s]". It is noted that even though the ligand is defined in the claim as an "ATP-binding site ligand", the claim does not require that the "ligand" be bound to the ATP-binding site of the recited protein and the breadth of structures of the "ATP-binding site ligand[s]" as encompassed by the claims are undefined and unlimited. Consequently, the scope of recited crystals encompasses crystals of a protein in complex with *any* "ATP-binding site ligand" having any structure. As noted in a prior Office action, the specification discloses only a single working example of a crystal as encompassed by the claims, *i.e.,* a crystal of residues 24-295 of SEQ ID NO:3 in complex with ATPγS having the space group symmetry $P6_122$ and having vector lengths a=b=80.45 Å, and c=172.18 Å (p. 24, Table 6) and method for its crystallization, *i.e.,* the method disclosed at p. 48, ¶¶ [00198] and [0199] of the specification. Other than this single working example, the specification fails to provide any specific guidance for replacing the ligand of ATPγS with any other "ATP-binding site

ligand" with an expectation of achieving a diffraction-quality crystal that maintains the recited space group and unit cell dimensions. While applicant may argue that a skilled artisan would expect that co-crystallizing the recited protein in complex with any other "ATP-binding site ligand" under the disclosed conditions would result in a crystal as encompassed by the claims, there is no evidence of record to support this position and the state of the art at the time of the invention would suggest otherwise. For example, a common method of obtaining a crystal with a ligand other than that of an initial crystal is to soak a crystal of a liganded protein with a different ligand. However, without analysis of the resulting crystal, there is no way to predict *a priori* whether the resulting crystal will maintain the space group and unit cell dimensions of the parent crystal prior to ligand soaking. See, *e.g.,* Skarzynski et al. (*Acta Crystallogr D Biol Crystallogr* D62:102-107), which discloses, "crystals of complexes obtained by compound soaking may become damaged, change their diffraction properties or even change the space group during the soaking experiment" (p. 103, column 2, middle).

In view of the broad scope of the claims, particularly with respect to the "ATP-binding site ligand", the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all crystals and polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the

claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[18] Status of the claims:

- Claims 1, 4, 9, 12, 15, 17-18, 22-25, and 27-36 are pending.
- Claims 18 and 22-25 are withdrawn from further consideration.
- Claims 1, 4, 9, 12, 15, 27-29, and 32-33 are rejected.
- Claims 17, 30-31, and 34-36 appear to be in a condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner

Art Unit 1656